REMARKS

I. Status of Claims

Claims 64, 65, 70-82, and 85-97 are currently pending in the application. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.

II. Claim Objections

The Office objected to claims 86 and 89 because of minor informalities. Office Action at pages 2-3. Claims 86 and 89 have been amended to address these informalities. Accordingly, Applicants request the Office to withdraw these objections.

III. Rejections Under 35 U.S.C. §112, Second Paragraph

1. Claims 64, 65, 70-82, and 85-97

The Office rejects claims 64, 65, 70-82, and 85-97 under § 112, second paragraph for alleged indefiniteness. Office Action at page 3. In particular the Office asserts that it is unclear what an amino acid corresponding to Y410, T542, D543, K593, Y595, Y385, G387, and G388 of Pfu DNA polymerase is. *Id.* According to the Office:

> The basis of the indefiniteness is two fold. First the recited amino acid positions are unclear with respect to "an amino acid position corresponding to" and second it is unclear what each of the recited positions refers to absent a specific amino acid sequence, such as SEQ ID NO:

Id. Applicants respectfully traverse this rejection.

As to the first point raised by the Office, Applicants submit that given the state of the art and the conserved nature of the domains recited in the claims, one of skill in the art would readily understand which amino acids in the second DNA polymerase correspond to the recited Pfu DNA polymerase residues.

The claims recite that the second DNA polymerase comprises:

the partitioning domain sequence YXGG (SEQ ID NO:6)[1] or SYTGGF (SEQ ID NO:7)[2];

the polymerase domain sequence DXXSLYP (SEQ ID NO:1);

the polymerase domain sequence YIDTDG (SEQ ID NO:21); and

the polymerase domain sequence KXY.

As disclosed in the specification and known in the art, these partitioning and polymerase domain sequences are common to a number of Archaeal DNA polymerases, including Pfu, Tgo, KOD, Tli, and Deep Vent (see pages 20-22 and 27-29). In addition, Applicants have compared the sequences of those Family B DNA polymerases taught in the specification at pages 14-19, and found that the now claimed domain sequences (or minor variants thereof) are found in each of the polymerases taught. Moreover, it was known in the art, at the time the instant application was filed, that the recited domain sequences (or consensus sequences thereof) are common to an even larger number of Archaeal DNA polymerases, including S. *solfataricus* MT4, S. *solfataricus* P2, S. *acidocaldarius, Thermococcus* 9oN-7, *Methanococcus voltae,* and *Methanococcus jannaschi* (*see, e.g.*, Edgell et al. 1997, J. Bacteriology 179:2632; Hopfner et al.,

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[1] Claim 64 and claims depending therefrom.

[2] Claim 86 and claims depending therefrom.

1999 Proc. Nati. Acad. Sci. 96:3600), in addition to those taught in the specification.

Furthermore, the amino acid sequence of the wild type Pyrococcus furiosis (Pfu) DNA polymerase was known and published under Accession Number P80061 and Genbank Accession Number U84155. *See* Specification at page 12, lines 8-9; page 16; and page 26, lines 11-12. The residues recited in the claims (Y410, T542, D543, K593, Y595, Y385, G387, and G388) represent amino acid residues in the known, wild type Pfu amino acid sequence, with each residue falling into one of the conserved polymerase or partitioning domains recited in the claims.

Specifically, Y410 falls within the polymerase domain sequence DXXSLYP; T542 and D543 fall within the YIDTDG polymerase domain sequence; K593 and Y595 fall within the KXY polymerase domain sequence; and Y385, G387, and G388 fall within the partitioning domain sequence YXGG or SYTGGF. Because the polymerase domain sequences and the partitioning domain sequence are conserved among Family B DNA polymerases, one of skill in the art would readily understand which amino acid residues in the second DNA polymerase correspond to the recited Pfu DNA polymerase residues. By way of example, Tables 2A and 2B identify the specific residues in the Tgo, KOD, Tli, and Deep Vent DNA polymerase that correspond to the Pfu amino acid residues recited in the claims. Specification at pages 27-29. Therefore, given the state of the art and the conserved nature of the domains recited in the claims, one of skill in the art could readily identify the amino acid residues of other DNA polymerases that correspond to amino acid residues Y410, T542, D543, K593, Y595, Y385, G387, and G388 of the Pfu DNA polymerase.

As to the Office's second point regarding the specific amino acid sequence of the Pfu DNA polymerase, Applicants submit that because the amino acid sequence of the Pfu DNA polymerase was known as of the filing date of the instant application (*see e.g.*, Specification at page 12, lines 8-9; page 16; and page 26, lines 11-12), the metes and bounds of the claims are clear. Applicants note that the written description requirement does not require an Applicant to recite or incorporate by reference known genes or sequences. *See Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1368 (Fed. Cir. 2006) (holding that "where, as in this case, accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences . . ., satisfaction of the written description requirement does not require either the recitation or incorporation by reference (where permitted) of such genes and sequences." Just as the written description requirement does not require the recitation of known sequences to convey to one of skill in the art that Applicants were in possession of the invention, Applicants submit that 35 U.S.C. 112, second paragraph, does not require the recitation of a specific amino acid sequence to delineate the metes and bounds of claimed subject matter when the amino acid sequence was known in the art. As one of skill in the art would have in mind the actual amino acid sequence of the known Pfu DNA polymerase, there is nothing unclear about the scope of the claims.

Nevertheless, while not acquiescing to the rejection, Applicants have amended the claims to recite the "wild type" Pfu DNA polymerase "identified at Accession No. P80061." Support for this amendment is found throughout the specification, including, for example, at page 26. This amendment makes explicit what was already implicit in the claim and does not change the claim's scope. Applicants respectfully request that the Office withdraw this rejection.

The Office also rejects claims 64, 65, 70-82, and 85-97 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite because they "recite 'reduced 5'-3' DNA polymerization activity' which is relative terminology and it is unclear what the reduced 5'-3' DNA polymerization activity is relative to." Office Action at page 3. As discussed in the specification, "reduced polymerization activity" refers to a DNA polymerization activity that is lower than that of the wild type enzyme. *See* Specification at page 10. Applicants have amended claims 64, 85, and 86 to recite that the second enzyme possesses reduced 5' - 3' polymerization activity as compared to the wild type form of the second enzyme, making explicit what was already implicit in the claims. Applicants respectfully request that the Office withdraw this rejection.

2. Claim 65

The Office rejects claim 65, which recites "said DNA polymerase" of claim 64, alleging that it is unclear which of the two different DNA polymerases of claim 64 is referred to. Office Action at page 4. Applicants have amended claim 64 to refer to a second DNA polymerase and have also amended claim 65 to refer to "said second DNA polymerase" thereby obviating this rejection.

3. Claims 70 and 82

The Office rejects claims 70 and 82 because they refer to the enzyme mixture of claim 67, and claim 67 has been cancelled. *Id.* Applicants have amended claims 70 and 82 to depend from claim 65, rendering this rejection moot.

4. Claim 74

The Office rejects claim 74 as allegedly indefinite, asserting that there is no antecedent basis for "said mutant JDF-3 DNA polymerase of claim 73." *Id.* Applicants have amended claim 74 to recite wherein "said second enzyme" contains an amino acid substitution at an amino acid position corresponding to G387 of Pfu DNA polymerase, rendering this rejection moot. Applicants have similarly amended claim 88.

IV. Rejection of Claims 64-94 Under 35 U.S.C. § 112, First Paragraph

1. Written Description

The Office rejects claims 64, 65, 70-82, and 85-97 under § 112, first paragraph for allegedly containing subject matter that is not supported by the specification at the time of filing. Office Action at page 4. Applicants respectfully traverse this rejection.

The Office asserts that "applicants have not adequately described the genus of those enzymes which comprise 5'-3' polymerization activity of a DNA polymerase or reverse transcriptase, beyond those enzymes which are a DNA polymerase or reverse transcriptase." *Id.* at 6. Although Applicants respectfully disagree with the Office, in an effort to expedite prosecution, claims 64 and 85 have been amended to recite that said first enzyme comprises a "first DNA polymerase or a reverse transcriptase having 5' - 3' polymerization activity." Applicants accordingly request that this portion of the rejection be withdrawn.

In a second aspect of this rejection, the Office further asserts:

> While applicants amendment of the recited mutant DNA polymerase to

> require certain structural domains is helpful in overcoming the rejection, it remains that applicants have not adequately described the referred to mutant DNA polymerases. Specifically with respect to the structure to function description of these mutants.

Id.

A description as filed is presumed to be adequate, unless and until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut that presumption. *See In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971); *see also*, M.P.E.P. § 2163.04. The burden is on the Office to establish a prima facie case of unpatentability by a preponderance of the evidence. *Id.*

In rejecting a claim, the Office must set forth express findings of fact which support the lack of written description conclusion. M.P.E.P. § 2163.04. These findings should:

(A) Identify the claim limitation(s) at issue; and

(B) Establish a *prima facie* case by providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed.

Here, the Office does not set forth any findings of fact to support this aspect (i.e., the second DNA polymerase) of the written description rejection. Specifically, the Office does not identify the claim limitation(s) at issue. What is it about the recited second DNA polymerase that is not adequately described? Nor does the Office provide any evidence or reasoning to support its assertion that one of skill in the art would have recognized that Applicants were not in

possession of the second DNA polymerase recited in the claims. Rather, the Office summarily concludes that "applicants have not adequately described the referred to mutant DNA polymerases. Specifically, with respect to the structure to function description of these mutants." Office Action at page 6. If the Office takes the position that the specification does not disclose a relationship between structure and function, the Examiner provides no explanation or evidence to support the assertion. Accordingly, the rejection should be reversed on this ground alone.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species. M.P.E.P. §2163.05. Here the specification discloses over 60 mutant DNA polymerases in Tables 2A and 2B found at pages 27-29 of the specification and in Table 1 at pages 53-55 of the specification. Applicants submit that this disclosure provides a representative number of species sufficient to satisfy the written description requirement.

The written description requirement for a genus may also be satisfied through the disclosure of one or more common features shared by the genus. The Federal Circuit, adopting a portion of the PTO's Written Description Guidelines, has provided the following guidance regarding what constitutes adequate written description for claims drawn to biological sequences:

> The written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics."

Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 964, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002).

The claims at issue define the second DNA polymerase by both structure and by functional characteristics coupled with a known or disclosed correlation between function and structure. As to the structure, the claims recite that the second DNA polymerase comprises:

the partitioning domain sequence YXGG (SEQ ID NO:6);

the polymerase domain sequence DXXSLYP (SEQ ID NO:1);

the polymerase domain sequence YIDTDG (SEQ ID NO:21); and

the polymerase domain sequence KXY.

As disclosed in the specification and known in the art, these partitioning and polymerase domain sequences are common to a number of Archaeal DNA polymerases, including Pfu, Tgo, KOD, Tli, and Deep Vent (see pages 20-22 and 27-29). In addition, Applicants have compared the sequences of those Family B DNA polymerases taught in the specification at pages 14-19, and found that the now claimed domain sequences (or minor variants thereof) are found in each of the polymerases taught. Moreover, it was known in the art, at the time the instant application was filed, that the recited domain sequences (or consensus sequences thereof) are common to an even larger number of Archaeal DNA polymerases, including S. *solfataricus* MT4, S. *solfataricus* P2, S. *acidocaldarius, Thermococcus* 9oN-7, *Methanococcus voltae,* and *Methanococcus jannaschi* (*see, e.g.*, Edgell et al. 1997, J. Bacteriology 179:2632; Hopfner et al., 1999 Proc. Nati. Acad. Sci. 96:3600), in addition to those taught in the specification. The claims thus recite sufficiently detailed, relevant identifying characteristics to describe the genus of DNA polymerases that are modified to arrive at the second DNA polymerase of the claims.

The claims also recite that the second DNA polymerase further comprises an amino acid substitution at an amino acid position selected from an amino acid position corresponding to Y410, T542, D543, K593, Y595, Y385, G387, and G388 of the wild type Pfu DNA polymerase. As disclosed in the specification, the amino acid sequence of the wild type Pfu DNA polymerase was known and published under Accession Number P80061 and Genbank Accession Number U84155. *See* Specification at page 12, lines 8-9; page 16; and page 26, lines 11-12. The residues recited in the claims (Y410, T542, D543, K593, Y595, Y385, G387, and G388) represent amino acid residues in the known Pfu amino acid sequence, with each mutation falling into one of the conserved polymerase or partitioning domains recited in the claims, as noted above. Because the polymerase domain sequences and the partitioning domain sequence are conserved among Family B DNA polymerases, one of skill in the art would readily understand which amino acid residues in the second DNA polymerase correspond to the recited Pfu DNA polymerase residues, as demonstrated, for example, in Tables 2A and 2B.

The dependent claims provide additional structural contours to the claimed subject matter, referring to DNA polymerases whose amino acid sequences were known as of Applicants' filing date. Dependent claims 65, 70, and 82 further recite that the second DNA is derived from a DNA polymerase selected from Tli DNA polymerase (Vent DNA polymerase), PGB-D (Deep Vent) DNA polymerase, Tgo DNA polymerase, Pfu DNA polymerase, KOD DNA polymerase, and JDF-3 DNA polymerase having the sequence of SEQ ID NO. 10. Dependent claims 71 and 72 further recite that the second DNA polymerase is from the species *Pyrococcus kodakaraensis* and comprises an amino acid substitution at certain recited residues. Dependent

claims 73 and 74 recite that the second DNA polymerase has the amino acid sequence of SEQ ID NO. 10 and comprises an amino acid substitution at certain recited residues. Dependent claims 76-78 and 96 recite that the second DNA polymerase is from the species *Pyrococcus furiosis* and comprises an amino acid substitution at certain recited residues. Dependent claims 79-81 recite that the second DNA polymerase is a JDF-3 DNA polymerase or a DNA polymerase from the species *Pyrococcus kodakaraensis*. Dependent claims 89-90 recite that the second DNA polymerase is from the species *Thermococcus gorgonarius* and comprises an amino acid substitution at certain recited residues. Dependent claims 91-92 recite that the second DNA polymerase is from the species *Thermococcus litoralis* and comprises an amino acid substitution at certain recited residues. Dependent claims 95 and 97 recite that the second DNA polymerase is from a bacterium in the division Archaea.

Finally the claims recite that the second DNA polymerase has 3' -5' exonuclease activity and reduced 5' - 3' DNA polymerization activity as compared to the wild type form of the second enzyme. As disclosed in the specification, DNA polymerases with 3' - 5' exonuclease activity (exo+) can be modified within the polymerase and partitioning domains recited in the claims to generate modified DNA polymerases having reduced 5' - 3' DNA polymerization activity that still retain their 3' - 5' exonuclease activity. *See* Specification at pages 19-26. Thus, contrary to the Office's unsupported assertions, there is a disclosed correlation between structure and function. The specification also describes how to measure those functional characteristics using routine methods known in the art. Specification at pages 29-33 and 57-59.

Accordingly, the second DNA polymerase of the claims sets forth structure, i.e., the recited polymerase and partitioning domains (or the known DNA polymerases in the dependent claims) comprising one or more of the amino acid substitution recited in the claims, coupled with a disclosed correlation with function, i.e., 3' - 5' exonuclease activity and reduced 5' - 3' DNA polymerization activity. *See Enzo Biochem,* 323 F.3d at 964, 63 USPQ2d at 1613. In this way, the specification provides a description of the second DNA polymerase in sufficient detail so that one of skill in the art would recognize that Applicants had invented the claimed subject matter. Based on the disclosure in the specification and state of the art at the time the instant application was filed, Applicants have demonstrated that they were in possession of the invention recited in the amended claims and, accordingly, request that the rejection be reconsidered and withdrawn.

2. Enablement

The Office also rejects claims 64, 65, 70-82, and 85-97 under §112, first paragraph, for alleged overbreadth. Office Action at pages 6-7. The Office Action states that the specification does not provide sufficient teachings to enable one of skill in the art to practice the claimed invention with any enzyme mixture comprising a first enzyme with a polymerization activity of a DNA polymerase or reverse transcriptase and a second DNA polymerase comprising certain recited polymerase and partitioning domains and one or more mutations corresponding to Y410, T542, D543, K593, Y595, Y385, G387, or G388 of Pfu DNA polymerase. *Id.* Applicants respectfully disagree and traverse the rejection.

With respect to the enablement of a first enzyme having a 5' - 3' activity of a DNA polymerase or reverse transcriptase, as noted above, Applicants have amended the claims to

recite that the first enzyme is a DNA polymerase or a reverse transcriptase having 5' - 3' polymerization activity. The instant specification teaches, and it is well known in the art that 5' - 3' polymerization activity is possessed by all DNA polymerases. Thus, between the teachings in the specification and the general knowledge in the art, Applicants have enabled numerous species of DNA polymerases or reverse transcriptases having 5' - 3' DNA polymerization activity, such that one of skill in the art could readily practice the invention with respect to the first enzyme without having to engage in undue experimentation.

The Office Action also states that the claims are rejected with respect to the second enzyme, a DNA polymerase comprising the partitioning domain sequence YXGG, the polymerase domain sequence DXXSLYP, the polymerase domain sequence YIDTDG, and the polymerase domain sequence KXY, and having 3' - 5' exonuclease activity and reduced 5' - 3' DNA polymerization activity.

The Office has the initial burden of establishing a *prima facie* case of lack of enablement. M.P.E.P. § 2164.04. Applicants' specification disclosing how to make and use the claimed invention must be taken as complying with 35 U.S.C. § 112, first paragraph, unless there is reason to doubt the objective truth of the disclosure. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1437, 1442 (Fed. Cir. 1995). The Office has questioned the scope of enablement provided by Applicants' specification but has not given any technical reasons to support the rejection. As stated in *In re Marzocchi*, 169 USPQ at 369 (emphasis in original):

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its

> own with acceptable evidence or reasoning which is inconsistent with the contested statement.

Absent such evidence, the burden ***does not shift*** to the Applicants. *Id.*

The Specification provides numerous examples of mutant DNA polymerases in Tables 2A and 2B found at pages 27-29 of the specification and in Table 1 at pages 53-55 of the specification. The Office does not provide any evidence or reasoning why the specification does not enable those disclosed mutant polymerases. While the Office acknowledges that the recited structural domains are "helpful in identifying those encompassed mutant DNA polymerases," it asserts that "the recited structural domains required by the mutant DNA polymerases remain insufficient to enable the full scope of those DNA polymerase mutants encompassed by the claims. " Office Action at page 10. Notably, the Office provides no evidence or reasoning to support its assertions.

This stands in sharp contrast to the specification. As noted above, the specification in combination with the prior art, teaches that the recited partitioning and polymerase domain sequences are common to a number of Family B DNA polymerases, including the Archaeal DNA polymerases. It was well known in the art at the time the instant application was filed that members of the family of Archaeal DNA polymerases share common sequence motifs and domains that possess particular function. For example,

- Edgell et al. shows sequence alignments of 15 different Archaeal DNA polymerases, and identifies three exonuclease domains and seven polymerase domains, that play a role, respectively, in the exonuclease and polymerization

activity of the Archaeal DNA polymerases (Edgell et al., 1997 J. Bacteriol. 179:2632).

- Hopfner et al. teaches that the Archaeal DNA polymerases share a DTDG motif in the polymerase active site (Hopfner et al., 1999, PNAS 96:3600).
- Wang et al. prepared a sequence alignment of 24 Family B DNA polymerases, of which the Archaeal DNA polymerases are a subfamily, and teaches that the alignment shows 10 absolutely conserved and 96 consensus residues, three quarters of which "appear to play a role in the enzyme's structural integrity, while one-quarter may be directly involved in binding the dNTP and DNA primer-template substrates, as well as binding the metal ions required for both exonuclease and polymerase catalytic activities" (Wang et al., 1997, Cell 89: 1087).
- The specification provides specific guidance as to where mutations could be made in a DNA polymerase to reduce polymerization activity. For example, the specification teaches at page 21-22 that mutations in the partitioning and polymerase domains are likely to result in reduced polymerization activity.
- The specification also teaches that several investigators had already identified DNA polymerase mutations that selectively reduce DNA polymerization activity (Blanco et al., 1995 Methods of Enzymology 262:283-294 ((Bacteriophage 429); Truniger et al., 1996, EMBO J. 15:3430-3441 (Bacteriophage 429); Abdus Sattar et al., 1996, Biochemistry 35:16621-9

(Bacteriophage T4); Tuske et al., 2000, J. Biological Chemistry 275:23759-68 (Kienow fragment); Bohlke Ct al., 2000, Nucleic Acid Research 28:3910-3917 (Thermococcus aggregans); Pisani et al., 1998, Biochemistry 37:15005-15012 (Sulfolobus solfataricus); Komori Ct al., 2000, Protein Eng 13:41-7 (Pyrococcus furiosus); Shen et al., 2001 J. Biological Chemistry 276:27376-83 (Pyrococcus horikoshi Family D); these mutations being different from those recited in the instant claims).

This evidence stands unrebutted.

Moreover, the claims recite that the second DNA polymerase has 3' - 5' exonuclease activity and reduced 5' - 3' DNA polymerization activity. The Office summarily concludes that "[b]ecause of this lack of sufficient guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the desired activities, it would require undue experimentation for one skilled in the art to arrive at the majority of those enzyme mixtures of the claimed genus." Office Action at page 10. But again the Office does not provide any evidence or reasoning that one skilled in the art would not be able to test for the recited activity.

As noted above, methods for making the claimed mutant polymerases and screening for the recited activities were known in the art and disclosed in the specification. *See* Specification at pages 29-33 and 57-59. Given the working examples in the specification, the high level of skill in the art, and the state of the art itself, the experimentation involved to make and use other mutant polymerases falling within the scope of the claims, and thus practice the full scope of the

pending claims, would have been routine and well within the skill of those in the art. *See e.g.*, *Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1360, 47 USPQ2d 1705, 1719 (Fed. Cir. 1989 ("test [for undue experimentation] is not merely quantitative . . . if it is merely routine.").

The Office has not provided acceptable evidence or reasoning which is inconsistent with the specification, and, therefore, has not met the initial burden of showing that the claims are not enabled. *In re Marzocchi*, 169 USPQ at 369. Accordingly, Applicants request that this rejection be reconsidered and withdrawn.

V. Double Patenting

The Office Action states that claims 64-94 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 6, 9-14, 18, 20-22, and 36-51 of co-pending application USSN 10/035,091. Applicants will timely submit a terminal disclaimer to disclaim any term of the instant application that would extend beyond the expiration of the 10/035,091 application upon notification of allowable subject matter in the instant case, and upon confirmation that the claims, at that time, are patentably indistinct.

VI. Conclusion

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 50-3740.

Respectfully submitted,
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